II. REMARKS

Claims 53 – 61 and 63 – 93 were examined in the outstanding Office Action. By this Amendment and Reply, claims 65-67, 71, 72, 76, 77, 81 and 82 have been canceled without prejudice to pursuit of these claims in a later filed continuation application. Claims 53, 55-58, 63, 78-80, 83, 84 and 86 have been amended. Amended claims 53 - 61, 63, 64, 68-70, 73 — 75 and 83-93 presently are under examination.

Support for these amendments are found throughout the application papers, as indicated *infra*. Thus the amendments to the claims do not raise an issue of new matter and entry thereof is respectfully requested.

The specification also has been amended to correct typographical errors as noted by the Office and to correct errors in the spelling of deoxyuridine. The amendments to the specification do not raise an issue of new matter and therefore, entry thereof is respectfully requested.

In view of the preceding amendments and the remarks which follow, reconsideration and withdrawal of the outstanding rejections and objections is respectfully requested.

Information Disclosure Statements

The Examiner questioned the number of references Applicants' representative has submitted to assist the Office in examining the application. Applicants and their representative have to the best of their ability, complied with the requirements of 37 C.F.R. § 1.56 to disclose to the Office all information which may be material to the examination of the claims. Applicants' representative can not predict what the Office would consider "material" and therefore in an excess of caution, forwarded to the Office references (other than textbooks or manuals) and information that was utilized during the preparation of the application and the underlying inventions. Moreover, because the subject application has numerous related applications (which is noted by the Office in its rejections of the claims on the grounds of double patenting and obviousness-type double patenting) and foreign counterparts, references cited during the examination of these applications were also forwarded to the Office.

In accordance with their continuing duty of disclosure, Applicants enclose a Supplemental Information Disclosure Statement (IDS) for consideration and entry into the application file.

Objections to the Disclosure

The Office objected to the disclosure on the following grounds.

The disclosure on page 56, the title at lines 2-3 is missing the letter "o" in five separate locations.

Applicants confirm that this error is not in Applicants' copy and agree that the missing letters are likely the result of a scanning error. The complete title in the original copy is submitted herein to correct any errors that may exist in the title.

The Office noted that the structures identified at pages 43 and 44 as being either propargylic or allylic moieties do not match the description. Applicants have amended the structures accordingly.

The structures on pages 28, 29, and 30 have been amended to correct obvious clerical errors in their drawings.

The specification and claims have been amended in a sincere effort to remove the grounds for objection. In view of these amendments, reconsideration and withdrawal of the objections is respectfully requested.

35 U.S.C. § 112

Claims 53, 59 – 61, 63 – 72, 75 – 78 and 85 – 93 stand rejected under 35 U.S.C. § 112, first paragraph on the ground that the subject matter of these claims allegedly was not described in the specification in such a way as to enable one of ordinary skill in the art in the invention to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Office argued that the fundamental issue is whether practicing the full scope of the instant invention is possible without undue experimentation. The Office stated that the breadth

of the claims extends to compounds the synthesis of which has not been adequately supplied nor demonstrated in the treatment of neoplastic diseases.

With respect to claim 63, the Office alleged that :

i) the experimental examples do not show how to make compounds wherein R^1 is Cl, I or CN;

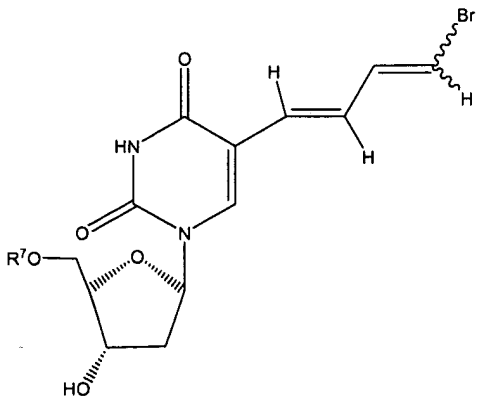
ii) the experimental examples do not show wherein R^7 is a phosphodiester group or a phosphoramidate group," and

iii) the experimental examples do not show compounds that can be in any enantiomeric, diastereoisomeric or stereoisomeric form,..... including L-form, α-anomeric form.

Also, the Office stated that some of the claims were not enabled because the specification does not show treatment of liver cancer.

Claim 63 further stands rejected under 35 U.S.C. § 112, second paragraph on the grounds that the terms "phosphodiester group" and "phosphoramidate group" allegedly are indefinite.

Applicants respectfully traverse for the reasons that follow. Amended claim 53 is directed to a compound having the structure:



wherein R^7 is a phosphate group, or a phosphoramidate group; wherein the phosphoramidate group consists of a phosphorous atom bound to 1) an oxygen atom, 2) to a hydroxy, phenoxy, or a substituted phenoxy group, and 3) to an amino acid, wherein the amino acid is bound to the phosphorous atom through its amino group and optionally bound to the 3' carbon of the sugar through its carboxy group; and pharmaceutically acceptable salts thereof.

Pending claims 54 to 61 depend directly or indirectly on claim 53 and therefore inherently possess all the limitations of claim 53.

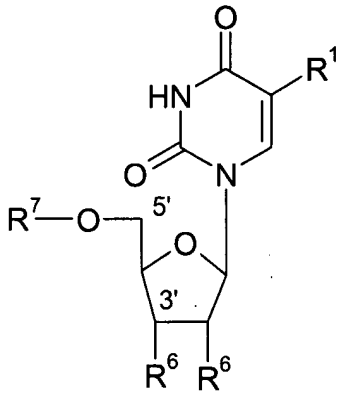
Applicants respectfully request withdrawal of the rejection as applied against claims 53 to 61. The compound specifically recites that R_1 is a bromodiene and has one of a specific chemical group attached to the 5' carbon. Therefore, the rejections numbered as paragraphs i) and ii) above do not apply to claims 53 to 61. With respect to the different "forms" of the compound, Applicants reassert that it would not require an undue amount of experimentation to make the various forms of the compound. However, because the Office has not specifically recited where the technical difficulty arises, especially in light of the fact that the "state of the prior art is well established by the extensive lists of the prior art patents and other references disclosed by the patents issued to Shepard and Shepard et al. listed on the instant PTO-892." (Quoted from paragraph "B" listed on page 4 of the Office Action.). Applicants respectfully request the a definitive, technically supported, statement of the grounds for this rejection.

With respect to liver cancer, the compound claims are not specifically directed to the treatment of liver cancer. For these reasons, removal of the ground for rejection as applied against claims 53 to 59 and 61.

With respect to claim 60, which does recited liver cancer, the claim depends on claim 59 which specifically recites that the cell being treated overexpress thymidylate synthase (TS). Applicants' specification teaches that the biological activity of the compounds are linked to the overexpression of TS in the cell, regardless of the type of cell. Enclosed for the Office's convenience is a copy of Voeller, R.L et al. "Elevated Levels of Thymidylate Synthase Linked to Cancer Etiology" CCR Frontiers in Science, Vol. 4, pages 6-7 (March 2005) which reports that not only have clinical studies shown that TS levels are elevated in cervical, breast, kidney, bladder, lung and gastrointestinal tumor tissues as compared to their normal counterpart, cellular transformation to the cancer phenotype **can be induced** by overexpression of TS in cells. Additionally, liver cancer cells are known to overexpress TS, (see Gonen, M. et al. "Thymidylate Synthase Expression in Hepatic Tumors is a Predictor of Survival and Progression in Patients with Resectable Metastatic Colorectal Cancer" J. Clin. Oncol. Vol. 21(3), pages 406-412 (Feb. 2003), copy enclosed) and that information, in combination with the evidence of efficacy supplied to the Office against other cancer cell types that overexpress TS, there is no objective

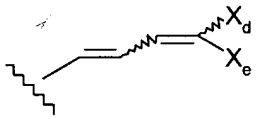
reason offered by the Office to doubt efficacy of the claimed compounds against liver cancer cells as long as they overexpress TS. For that reason, the rejection as applied against claim 60 is improper and Applicants respectfully request its withdrawal.

Applicants also request reconsideration and withdrawal of the grounds for rejection under 35 U.S.C. § 112, first paragraph as applied against claims 63 to 93. Independent claim 63 is directed in part to a compound having the structure:



wherein:

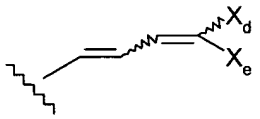
(i) R^1 is a group:



wherein X_d is H; and, X_e is Cl or Br;

or:

(ii) R^1 is a group:



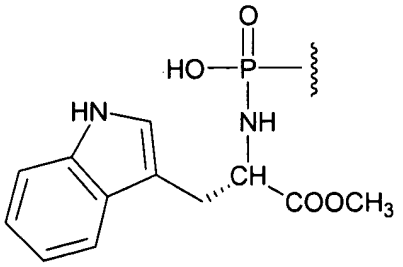
wherein X_d and X_e are independently the same or different and are selected from Cl, Br, I, and CN.

Claims 64 to 66 to 70, 73 to 75 and 73 to 86 are directed to compounds specifically falling within the scope of the above-noted compound. R^1 is therefore limited to dienes containing the halogens: Br or Cl or CF3 or H. The Office has not provided a reasoned statement why it is beyond one of skill in the art to make compounds having the halogen I or

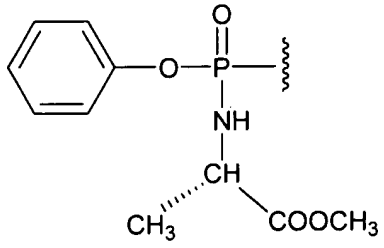
pseudohalogen (CN) using the information provided in the specification and known in the art. Applicants respectfully request this information so that they can address the substance of the Office's concerns.

Claim 63 has been amended so that the 2' R^6 group is limited to hydrogen; the 3' R^6 group is limited to hydroxy or can form a ring with the carboxy group of an R^7 amino acid group, and R^7 has been amended to includes either hydrogen, a phosphate group, or a phosphoramidate group. The term phosphoramidate group has been further clarified to include a phosphorous atom bound to 1) an oxygen atom , to 2) a hydroxy, phenoxy, or a substituted phenoxy group, and 3) to an amino acid, wherein the amino acid is bound to the phosphorous atom through its amino group and optionally bound to the 3' carbon of the sugar through its carboxy group.

An example of a phosphoramidate wherein R^7 is bound to an oxygen atom, a hydroxy group, and an amino acid is given on page 22:



Support for various phenoxy phosphoramidates are on page 19:

> "In an alternative embodiment, R^7 is a phosphoramidate group derived from an amino acid, including, for example, the twenty naturally occurring amino acids. In one embodiment, R^7 is or contains a group having the structure:
>
> 
>
>
> The above group, and methods for its synthesis, are described in McGuigan, et al. (1993), and McGuigan, et. al. (1996)."

McGuigan, et al. (1993), and McGuigan, et. al. (1996), which were previously submitted in the IDS, disclose not only phenoxy groups but also substituted phenoxy groups.

Support for phosphoramidates that form a cyclic ring with the sugar group and their synthesis is given on page 23.

The Office also rejected the claims on the ground that the identity or synthesis of the compounds on page 68 are incomplete. Applicants note that the compound identifiers on page 68 can be correlated to the table of R groups on pages 26 and 27, and to examples 1-16 on page 48-57.

With respect to the rejection under the second paragraph of 35 U.S.C. § 112, Applicants first direct the Office's attention to § 2173.02 of the M.P.E.P., which states:

> The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in vacuum, but in light of:
>
> (A) The content of the particular application disclosure;
>
> (B) The teachings of the prior art; and
>
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

Phosphoramidates are generally disclosed as R^7 groups (for example, see original claim 1) and the disclosure points to McGuigan, et al. (1993) and McGuigan, et. al. (1996) as specific examples of phosphoramidates. One of skill in the art, upon reading amended claim 63 and the two aforementioned references, would understand that phosphoramidates include both substituted and unsubstituted phenoxy groups.

The Office also questions whether the psuedoatoms "CN" or "I" would produce equivalent biological results. NB1013 is the chlorine analog of the bromine compound NB1011 and shows similar activity in Table 5 on page 68. One of skill in the art would reasonably expect that similar pseudoatoms such as CN would produce similar results. Restriction of the claims to just Br or Cl would suggest that only tested compounds be claimed; Applicants are not aware of any legal theory that supports this requirement.

Claims 79, 80, 83, and 84 have been amended so that the structures are consistent with amended claim 63.

The Office further requested that the amendments previously made to claim 58 be made to claim 86. Claim 86 has been amended accordingly to include the term "pharmaceutical composition."

The Office also objected to the claims on the ground that the specification does not provide support for the synthesis of "any enantiomeric, diasteriomeric or steriosomeric form".

Applicants respectfully traverse and request the Office to provide specific, technical supported, statements for the assertion of non-enablement. Synthesis of the compounds encompassed by the newly amended claims uses many well known techniques and what is not known in the art is provided by Applicants' specification. Reconsideration and withdrawal of the rejection, in view of the amendments to the claims made herein, is respectfully requested.

Double Patenting

Claims 55 and 56 were rejected under 35 U.S.C. § 101 for allegedly claiming the same invention as that of claims 3 and 4 of prior U.S. Patent No. 6,683,061 (PTO-892 ref. AB). This is a double patenting rejection.

Claims 53-54, 57-86 and 91-93 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-2 and 5-10 of U.S. Patent No. 6,683,061 (PTO-892 ref. AB).

Claims 53-61, 63-86 and 91-93 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-6 and 28-30 of copending Application Serial No. 10/119,927.

Claims 53-86 and 91-93 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 56, 57 and 61 of copending Application Serial No. 09/782,721.

The Office also remarked that some or all of claims 53 – 61, 63 – 86 and 91 - 93 of this application are alleged to conflict with claims 1-6 and 28-30 of copending Application Serial No. 10/119,927 and claims 56, 57 and 61 of copending Application Serial No. 09/782,721

Applicants respectfully defer responding to the above noted rejections until allowable subject matter has been indicated by the Office in the subject application.

III. CONCLUSION

Should the Patent Office determine that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-0872,** referencing attorney docket no. 060925-0801. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

If telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 251-1129.

Respectfully submitted,

Date Nov. 29, 2005

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